Q7 immunoglobulin light chain polypeptide sequence thereby producing said transgenic non-human animal.

REMARKS

In the Office Action dated November 8, 2000, claims 1-19 and 26-32 are under consideration. Claims 20-25 are withdrawn from consideration.

In response to the Office Action, Applicant has amended the claims which, when considered in view of the following remarks, is deemed to place the application in condition for allowance. Favorable consideration of all pending claims is respectfully requested.

In the Office Action, the Examiner has made the restriction requirement final. Consequently, claims 20-25 are withdrawn from consideration.

In response, Applicant has canceled claims 20-25 by way of the foregoing amendment. Applicant reserves the right to file a divisional application to pursue the subject matter of these canceled claims.

Claims 11-18 and 26-32 are rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled.

The Examiner admits that the specification is enabling for a transgenic rabbit comprising a portion of functional human heavy chain immunoglobulin genes, wherein the portion of functional heavy chain immunoglobulin genes comprises at least one constant region and at least one variable region, and wherein said variable region element is the variable region element proximal to the D region. The Examiner also admits that the specification is enabling for a transgenic rabbit comprising at least a portion of functional human light chain immunoglobulin genes, wherein the human immunoglobulin light chain gene encodes the κ chain. The Examiner further admits that the specification is enabling for methods of producing such transgenic rabbits. In addition, the Examiner admits that the specification is enabling for a

transgenic mouse comprising the same transgenes (i.e., a portion of functional human heavy chain immunoglobulin genes or a portion of functional human light chain immunoglobulin genes), as well as methods of producing such transgenic mice by homologous recombination in embryonic stem cells.

However, the Examiner contends that the specification does not reasonably provide enablement for all transgenic non-human animals comprising any of all functional heavy chain immunoglobulin genes, or any of all functional light chain immunoglobulin genes, or for methods of making the same transgenic animals.

Applicant respectfully disagrees with the Examiner. Applicant submits that those skilled in the art are fully enabled to make any transgenic nonhuman animal as claimed in view of the present teachings. However, in an effort to favorably advance the prosecution of the present application, Applicant has amended claims 11-12, 14-18, 26-28 and 30-32 to further characterize the transgenic non-human animal as one "which generates antibody diversity predominantly by gene conversion". Claims 4 and 14, have been canceled without prejudice.

Applicant respectfully submits that the present specification adequately teaches how to make a transgenic non-human animal which generates antibody diversity predominantly by gene conversion. For example, at page 5, lines 25-27, it is taught that in animals which gene convert (e.g., rabbits, pigs, sheep and cattle), replacement of the V region element proximal to the D region with a human V region element will result in the expression of the human V region element in the majority of immunoglobulins. Thus, the genetic engineering approach of making a transgenic animal which gene converts is substantially easier than the approaches that have been used in making transgenic mice. The specification further describes how to make a transgenic non-human animal which produces immunoglobulins comprised of at least a portion

of a human immunoglobulin polypeptide sequence, at pages 6-9. In addition, the specification specifically exemplifies the procedure of making a transgenic rabbit at pages 11-12.

Accordingly, it is respectfully submitted that claims 11-12, 14-18, 26-28 and 30-32 as amended, drawn to transgenic non-human animals which generate antibody diversity predominantly by gene conversion and to methods of making such animals, are fully taught by the present specification. As such, the rejection of claims 11-18 and 26-32 under 35 U.S.C. §112, first paragraph, is overcome. Withdrawal of the rejection is respectfully requested.

Claims 1-19 and 26-32 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite.

More specifically, the Examiner contends that the term "predominantly" in claims 1 and 11 used to describe the constituents of the polyclonal antisera is vague. It is respectfully submitted that claims 1 and 11 have been amended to delete the term "predominantly".

The Examiner also contends that the term "substantially human" in claims 1, 11 and 26 does not convey a clear meaning. It is respectfully submitted that the meaning of the term "substantially human" in reference to immunoglobulin molecules is clear to those skilled in the art in view of the instant disclosure. However, in an effort to advance the prosecutionof the present application, claims 1, 11 and 26 have been amended to delete the term "substantially human".

Furthermore, the Examiner indicates that the recitation "transgenic" at line 1 of claim 2 lacks an antecedent basis. It is submitted that claim 1 has been amended to insert the term "transgenic" thereby providing the antecedent basis for claim 2.

The term "at least a portion of" as recited in claims 1-2, 5-6 and 11-12, the term "portion of" in claims 11 and 15-16, and the term "at least in part" in claim 11 are alleged to be

indefinite. The Examiner contends that it is unclear if all portions of human immunoglobulins are capable of antigen recognition.

It is respectfully submitted that the term "at least in part" in claim 11 has been replaced with the term "at least a portion of". It is further submitted that the claimed transgenic non-human animals produce immunoglobulin molecules comprising at least a portion of a human immunoglobulin polypeptide sequence. That is, the immunoglobulin molecules produced from the transgenic rabbit can be a fully human immunogloblulin molecule, or a chimeric immunoglobulin molecule, i.e., a molecule composed of both human immunoglobulin sequence and rabbit immunoglobulin sequence. The human immunoglobulin sequence introduced into antibody molecules of the transgenic rabbit can be an immunoglobulin variable region (which is involved in binding to antigen), or an immunoglobulin constant region (which is not involved in binding to antigen). Accordingly, the term "at least a portion of" of a human immunoglobulin sequence is clear to those skilled in the art.

The Examiner also contends that the recitation " substantially incapable of" in claims 26-27 is indefinite. It is respectfully submitted that claims 26-27 have been amended to delete the recitation "substantially incapable of producing endogenous antisera".

In view of the foregoing, it is respectfully submitted that the rejection of claims 1-19 and 26-32 under 35 U.S.C. §112, second paragraph, is overcome. Withdrawal of the rejection is respectfully requested.

Claims 1-10 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by Lonberg et al. (U.S. 5,874,299, filed 14 February, 1997). Claims 1-10 are directed to polyclonal antisera compositions of a transgenic nonhuman animal.

According to the Examiner, Lonberg et al. teach the production of polyclonal antisera that comprises at least a portion of the human heavy chain polypeptide, wherein the portion of the human heavy chain polypeptide comprises at least one constant region element and one variable region element. The Examiner alleges that the polyclonal antisera of Lonberg et al. can recognize any immunogen.

Applicant respectfully directs the Examiner's attention to the amendment to claims 1-10. Claims 1-2 and 4-10 as amended are drawn to a polyclonal antisera composition of a transgenic nonhuman animal which generates antibody diversity predominantly by gene conversion. Claim 3, which delineats the nonhuman animal as one which generates antibody diversity predominantly by gene conversion, has been canceled without prejudice.

Applicant respectfully submits that the polyclonal antisera compositions presently claimed are not taught by Lonberg et al. Applicant observes that the teaching of Lonberg et al. is limited to transgenic mice which produce antibodies encoded by immunoglobulin genes not found in the mouse genome, such as human immunoglobulin heavy and light chain regions. It is well known that mice generate antibody diversity predominantly by gene rearrangement. Unlike the present invention, Lonberg et al. do not teach transgenic nonhuman animals which generate antibody diversity by gene conversion.

The Examiner states that patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it. In this case, however, Applicant submits that a polyclonal antisera composition of a transgenic nonhuman animal which generates antibody diversity predominantly by gene conversion is distinct from a polyclonal antisera composition of a transgenic mouse.

Moreover, Applicant observes that Lonberg et al. do not even teach the making of a polyclonal antisera composition from a transgenic mouse. As stated by Lonberg et al., one objective of producing transgenic mice is to obtain B-cells from such mice for making monoclonal antibodies. See, Lonberg et al., column 3, lines 20-40. Thus, Lonberg et al. do not teach or suggestthe claimed polyclonal antisera compositions of transgenic rabbits.

Accordingly, it is respectfully submitted that the rejection of claims 1-10 under 35 U.S.C. §102(e) as allegedly anticipated by Lonberg et al. is overcome. Withdrawal of the rejection is respectfully submitted.

Claims 11-18 (to transgenic nonhuman animals) and 26-32 (to methods of producing a transgenic nonhuman animal) are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Lonberg et al. in view of Brem et al. (U.S. 5,639,457) and Stice et al. (*Theriogenology* 49: 129-138, 1998).

The Examiner contends that Lonberg et al. teach transgenic mice that comprise human immunoglobulin heavy chain regions or human immunoglobulin heavy chain regions. The Examiner further contends that Lonberg et al. also describe cross-breeding of mice comprising human immunoglobulin heavy chain regions and mice comprising human immunoglobulin light chain regions.

The Examiner admits that Lonberg et al. do not teach transgenic rabbits or methods of making transgenic rabbits by nuclear transfer. However, the Examiner contends that Brem et al. teach transgenic rabbits which comprise human immunoglobulin heavy chain regions and which are made by pronuclear injection. Furthermore, the Examiner contends that Stice et al. teach that methods of cloning animals (sheep, cattle, pigs, mice, and rabbits) were known in the art. For example, Stice et al. discuss the production of transgenic animals by injecting targeting

constructs into the nucleus of a donor cell, which can be either an embryonic fibroblast or an embryonic stem cell. Accordingly, the Examiner concludes that, in view of the teachings of Brem et al. and Stice et al., it would have been obvious for one ordinary skilled in the art to modify the teachings of Lonberg et al. by creating transgenic rabbits that comprise human immunoglobulin heavy and light chain regions with a reasonable expectation of success. The Examiner contends that one of ordinary skill would have been sufficiently motivated to make such modifications as it was an art recognized goal to produce humanized antibodies in a transgenic non-human animal.

Applicant submits that Lonberg et al. do not teach or suggest any means for making transgenic animals which generate antibody diversity by gene conversion. As submitted above, the genetic engineering approach of making a transgenic animal which generates antibody diversity by gene conversion is substantially easier than the approaches that have been used in making transgenic animals which generate antibody diversity by gene rearrangement (e.g., mice). For example, as the V region element primarily used in gene conversion is the V region element proximal to the D region, the replacement of the V region element proximal to the D region with a human V region element will result in the expression of the human V region element in the majority of immunoglobulins.

In addition, Lonberg et al. do not teach or suggest making transgenic animals which serve as a useful source for obtaining polyclonal antisera compositions. Instead, Lonberg et al. aim to provide transgenic mice as a source for making human monoclonal antibodies. See, Lonberg et al., column 3, lines 20-40. Thus, those skilled in the art would not have been motivated by the teachings of Lonberg et al. to make transgenic nonhuman animals which

generate antibody diversity by gene conversion and which produce polyclonal antisera comprising at least a portion of a human immunoglobulin polypeptide.

As to Brem et al., the reference teaches the introduction into the male pronucleus of a fertilized ovum of a pig or rabbit, of a DNA sequence coding for a single, rearranged antibody. Unlike the present invention, Brem et al. do not teach the production of a transgenic animal which gene converts (e.g., a rabbit) by introducing a DNA sequence of a portion of (unrearranged) human immunoglobulin gene into the animal genome, wherein the introduced human sequence rearranges with immunoglobulin sequences endogenous to the animal to produce functional immunoglobulins. Neither do Brem et al. provide any suggestion or motivation for those skilled in the art to make such a transgenic animal.

Although Stice et al. discuss the production of transgenic animals in general, Applicant submits that Stice et al. do not provide any suggestion or motivation for those skilled in the art to make a transgenic animal which comprises a portion of human immunoglobulin sequence.

In this regard, Applicant submits that the rejection of claimed subject matter under 35 U.S.C. §103 in view of a combination of prior art references requires that the suggestion to carry out the claimed invention must be found in the prior art, not in Applicant's disclosure. In re Vaeck, 947 F.2d 488, 492, 20 U.S.P.Q. 1438, 1442 (Fed. Cir. 1991). Nothing in the combination of the cited references, in the absence of hindsight, suggests making a transgenic nonhuman animal which generates antibody diversity by gene conversion and which comprises a portion of human immunoglobulin sequence, wherein the human sequence rearranges with immunoglobulin sequences endogenous to the rabbit to produce functional immunoglobulins.

Accordingly, the rejection of claims 11-18 and 26-32 under 35 U.S.C. §103(a) as allegedly unpatentable over Lonberg et al. in view of Brem et al. and Stice et al. is overcome. Withdrawal of the rejection is respectfully requested.

It is further submitted that claim 1 has also been amended to replace the recitation "at least a portion of human heavy chain polypeptide" with the recitation "at least a portion of a human immunoglobulin polypeptide sequence". Support for such amendment is found throughout the specification, e.g., at page 4, lines 13-22, and in original claims 11-12 and 26-27.

Moreover, Applicant has added claims 33-44 which are fully supported by the specification and originally filed claims. No new matter is introduced.

Specifically, claims 33-35 depend from claim 1 and further delineate the human immunoglobulin polypeptide sequence as a human light chain polypeptide sequence. Support for claims 33-35 is found throughout the specification, e.g., at page 4, lines 13-22, and in original claim 12.

Added claims 36-42 are drawn to polyclonal antisera compositions of a transgenic non-human animal which generates antibody diversity by gene conversion. The compositions of claims 36-42 are characterized as comprising immunoglobulin molecules comprised of at least a portion of a human immunoglobulin polypeptide sequence and at least a portion of an immunoglobulin polypeptide sequence endogenous to the animal. Support for claims 36-42 is apparent from the specification and the originally filed claims.

Added claims 43-44 are drawn to methods of producing a transgenic non-human animal which generates antibody diversity by gene conversion, wherein said animal comprises a portion of a human heavy chain sequence (claim 43) and a portion of a human light chain

sequence (claim 44), respectively. Support for claims 43-44 is found in original claims 11-12 and 26-27.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made**."

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

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Enclosure: Version with Markings to Show Changes Made

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 1-2, 4-8, 11-12, 14-32 have been amended as follows:

1. (Amended) A polyclonal antisera composition of a transgenic nonhuman animal [that specifically recognizes an immunogen] which generates antibody diversity predominately by gene conversion, wherein said antisera composition specifically recognizes an immunogen and [is comprised predominantly of substantially human] comprises immunoglobulin protein molecules comprised of at least a portion of a human [heavy chain] immunoglobulin polypeptide sequence, and wherein said [substantially human] immunoglobulin protein molecules specifically bind to said immunogen.

2. (Amended) The polyclonal antisera according to Claim 1, wherein said [transgenic nonhuman animal is immunized with said antigenic entity, weighs at least 1 kg and comprises at least a] portion of [functional] the human immunoglobulin polypeptide sequence is a portion of a human immunoglobulin heavy chain [immunoglobulin] polypeptide sequence [genes integrated by homologous recombination into its genome].

4. (Amended) The polyclonal antisera composition according to Claim 1 or 33, wherein said transgenic nonhuman animal is from the order *Lagomorpha*.

5. (Amended) The polyclonal antisera composition according to Claim [1] 2, wherein said portion of [functional] the human heavy chain [immunoglobulin genes] polypeptide sequence comprises [at least one] a polypeptide sequence encoded by a human heavy chain constant region element.

6. (Amended) The polyclonal antisera composition according to Claim 5, wherein said portion of [functional] the human heavy chain [immunoglobulin genes] polypeptide sequence further

comprises [at least one] a polypeptide sequence encoded by a human heavy chain variable region element.

7. (Amended) The polyclonal antisera composition according to Claim 6, wherein said human variable region element [is] has replaced the endogenous variable region element proximal to the D region.

8. (Amended) The polyclonal antisera composition according to Claim 1, wherein said immunogen comprises a disease causing organism or antigenic portion [thereof] of said organism.

11. (Amended) A transgenic nonhuman animal [weighing at least 1 kg and] which generates antibody diversity predominately by gene conversion, comprising at least a portion of functional human heavy chain immunoglobulin genes integrated by homologous recombination into [its] the genome of said animal, wherein said portion of the functional human heavy chain immunoglobulin genes rearranges in frame with immunoglobulin heavy chain [immunoglobulin] sequences endogenous to said nonhuman animal to encode functional [, substantially human] antibody molecules that comprise at least [in part] a portion of a human immunoglobulin heavy chain [immunoglobulin] polypeptide [sequences] sequence, and wherein said animal [predominantly] produces said functional [, substantially human] antibody molecules when immunized.

12. (Amended) A transgenic nonhuman animal [weighing at least 1 kg and] which generates antibody diversity predominately by gene conversion, comprising at least a portion of functional human immunoglobulin light chain [immunoglobulin] genes integrated by homologous recombination into [its] the genome of said animal, wherein said portion of the human immunoglobulin light chain [immunoglobulin] genes [rearrange] rearranges in frame with immunoglobulin light chain sequences endogenous to said nonhuman animal to encode functional [, substantially human] antibody molecules that comprise at least [in part] a portion of a human immunoglobulin light chain [immunoglobulin] polypeptide [sequences]

sequence, and wherein said animal produces said functional antibody molecules when immunized.

14. (Amended) The transgenic nonhuman animal according to Claim 11 or 12, wherein said transgenic nonhuman animal is from the order *Lagomorpha*.

15. (Amended) The transgenic nonhuman animal according to Claim 11, wherein said portion of the functional human immunoglobulin heavy chain [immunoglobulin] genes comprises at least one human heavy chain constant region element.

16. (Amended) The transgenic nonhuman animal according to Claim 15, wherein said portion of the functional human immunoglobulin heavy chain [immunoglobulin] genes further comprises at least one human heavy chain variable region element.

17. (Amended) The transgenic nonhuman animal according to Claim 16, wherein said human variable region element [is] has replaced the endogenous variable region element proximal to the D region.

18. (Amended) The transgenic nonhuman animal according to Claim 12, wherein said portion of the human immunoglobulin light chain [gene] genes encodes the κ chain.

19. (Amended) An antisera composition produced by the transgenic nonhuman animal according to any one of [Claim 11] claims 11-18.

26. (Amended) A method of producing a transgenic nonhuman animal [weighing at least 1 kg and] which generates antibody diversity predominately by gene conversion, comprising at least a portion of human immunoglobulin genes integrated [by homologous recombination] into [its] the genome of the non-human animal, wherein said transgenic nonhuman animal [predominantly] produces functional [, substantially human] antibody molecules comprised [at least in part] of at least a portion of a human immunoglobulin polypeptide [sequences] sequence when immunized, said method comprising:

producing a first mutated animal neonate which comprises [comprising] immunoglobulin heavy chain [immunoglobulin] loci [where] wherein at least one of a constant region element or a [and/or] variable region element [elements are] endogenous to the non-human animal is replaced with [at least] a [functional portion of the] human heavy chain [immunoglobulin locus] constant region element or a human heavy chain variable region element, by [genetic alteration of] genetically altering a cell nucleus of [said] the non-human animal, introducing [said] the genetically altered cell nucleus into [an] a first enucleated nuclear transfer unit cell [to provide a first embryonic stem cell], and introducing [said] the first nuclear transfer unit cell which comprises the genetically altered nucleus into a female recipient host to produce [a] said first mutated neonate;

producing a second mutated animal neonate which comprises [comprising] immunoglobulin light chain [immunoglobulin] loci [where] wherein at least one of a constant region element or a [and/or] variable region element [elements are] endogenous to the non-human animal is replaced with [at least] a [functional portion of the] human light chain [immunoglobulin locus] constant region element or a human light chain variable region element, by [genetic alteration of] genetically altering a cell nucleus of [said] the non-human animal, introducing [said] the genetically altered cell nucleus into [an] a second enucleated nuclear transfer unit cell [to provide a second embryonic cell stem cell], introducing [said] the second nuclear transfer unit cell which comprises the genetically altered nucleus into a female recipient host to produce a second mutated neonate; [and] breeding mature first and second mutated neonates and selecting a transgenic non-human animal [animals capable of producing substantially human antisera and being at least substantially incapable of producing endogenous antisera] which produces functional antibody molecules comprised of at least a portion of a human immunoglobulin polypeptide sequence when immunized.

27. (Amended) A method of producing a transgenic nonhuman animal [weighing at least 1 kg and] which generates antibody diversity predominately by gene conversion, comprising at least a portion of human immunoglobulin genes integrated [by homologous recombination] into [its] the genome of the non-human animal, wherein said transgenic non-human animal [predominantly] produces functional [, substantially human] antibody molecules comprised [at least in part] of at least a portion of a human immunoglobulin heavy chain polypeptide

[sequences] sequence and at least a portion of a human immunoglobulin light chain polypeptide sequence when immunized, said method comprising:

producing a mutated animal neonate which comprises immunoglobulin heavy and light chain [immunoglobulin] loci [where] wherein at least one of a heavy chain constant region element or a heavy chain [and/or] variable region element [elements are] endogenous to the non-human animal is replaced with [at least a functional portion or the] a human heavy [and/or light] chain [immunoglobulin locus] constant region element or a human heavy chain variable region element, and wherein at least one of a light chain constant region element or a light chain variable region element endogenous to the non-human animal is replaced with a human light chain constant region element or a human light chain variable region element, by [genetic alteration of] genetically altering a cell nucleus of [said] the non-human animal, introducing [said] the genetically altered cell nucleus into an enucleated nuclear transfer unit cell [to provide a embryonic cell stem cell], and introducing [said] the nuclear transfer unit cell which comprises the genetically altered cell nucleus into a female recipient host to produce said mutated neonate; [and

breeding mature mutated neonates and selecting animals capable of producing substantially human antisera and at least substantially incapable of producing endogenous antisera] growing said mutated neonate, and determining said neonate as capable of producing antibody molecules comprised of at least a portion of a human immunoglobulin heavy chain polypeptide sequence and at least a portion of a human immunoglobulin light chain polypeptide sequence thereby producing said transgenic non-human animal.

30. (Amended) A method according to Claim 26, wherein said first mutated neonate comprises a heavy chain locus [comprises] wherein at least one constant region element endogenous to the non-human animal is replaced with a human heavy chain constant region element.

31. (Amended) A method according to Claim 26, wherein said first mutated neonate comprises a heavy chain locus [comprises] wherein at least one variable region element endogenous to the non-human animal is replaced with a human heavy chain variable region element.

32. (Amended) A method according to Claim [26] 31, wherein said [heavy chain locus comprises the] variable region element endogenous to the non-human animal is the variable region element proximal to the D region.

Please add the following claims:

33. The polyclonal antisera according to Claim 1, wherein said portion of the human immunoglobulin polypeptide sequence is a portion of a human immunoglobulin light chain polypeptide sequence.

34. The polyclonal antisera composition according to Claim 33, wherein said portion of the human light chain polypeptide sequence comprises a polypeptide sequence encoded by a human light chain constant region element.

35. The polyclonal antisera composition according to Claim 33, wherein said portion of the human light chain polypeptide sequence further comprises a polypeptide sequence encoded by a human light chain variable region element.

36. A polyclonal antisera composition of a transgenic non-human animal which generates antibody diversity predominately by gene conversion, comprising immunoglobulin protein molecules comprised of at least a portion of a human immunoglobulin polypeptide sequence and at least a portion of an immunoglobulin polypeptide sequence endogenous to the animal, wherein said immunoglobulin protein molecules specifically recognize an immunogen.

37. The polyclonal antisera composition according to Claim 36, wherein said portion of the human immunoglobulin polypeptide sequence is a portion of a human heavy chain polypeptide sequence.

38. The polyclonal antisera composition according to Claim 37, wherein said portion of the human heavy chain polypeptide sequence comprises a polypeptide sequence encoded by a human heavy chain constant region element.

39. The polyclonal antisera composition according to Claim 38, wherein said portion of the human heavy chain polypeptide sequence further comprises a polypeptide sequence encoded by a human heavy chain variable region element.

40. The polyclonal antisera composition according to Claim 36, wherein said portion of the human immunoglobulin polypeptide sequence is a portion of a human light chain polypeptide sequence.

41. The polyclonal antisera composition according to Claim 40, wherein said portion of the human light chain polypeptide sequence comprises a polypeptide sequence encoded by a human light chain constant region element.

42. The polyclonal antisera composition according to Claim 41, wherein said portion of the human light chain polypeptide sequence further comprises a polypeptide sequence encoded by a human light chain variable region element.

43. A method of producing a transgenic non-human animal comprising at least a portion of human immunoglobulin genes integrated into the genome of the animal, wherein said transgenic non-human animal generates antibody diversity predominately by gene conversion and produces functional antibody molecules comprised of at least a portion of a human immunoglobulin heavy chain polypeptide sequence when immunized, said method comprising:

producing a mutated animal neonate which comprises immunoglobulin heavy chain loci wherein at least one of a heavy chain constant region element or a heavy chain variable region element endogenous to the animal is replaced with a human heavy chain constant region element or a human heavy chain variable region element, by genetically altering a cell nucleus of the animal, introducing the genetically altered cell nucleus into an enucleated nuclear transfer unit cell, and introducing the nuclear transfer unit cell which comprises the genetically altered cell nucleus into a female recipient host to produce said mutated neonate;

growing said mutated neonate and determining the neonate as capable of producing antibody molecules comprised of at least a portion of a human immunoglobulin heavy chain polypeptide sequence thereby producing said transgenic non-human animal.

44. A method of producing a transgenic non-human animal comprising at least a portion of human immunoglobulin genes integrated into the genome of said rabbit, wherein said transgenic non-human animal generates antibody diversity predominately by gene conversion and produces functional antibody molecules comprised of at least a portion of a human immunoglobulin light chain polypeptide sequence when immunized, said method comprising:

producing a mutated animal neonate which comprises immunoglobulin light chain loci wherein at least one of a light chain constant region element or a light chain variable region element endogenous to the animal is replaced with a human light chain constant region element or a human light chain variable region element, by genetically altering a cell nucleus of the animal, introducing the genetically altered cell nucleus into an enucleated nuclear transfer unit cell, and introducing the nuclear transfer unit cell which comprises the genetically altered cell nucleus into a female recipient host to produce said mutated neonate;

growing said mutated neonate and determining the neonate as capable of producing antibody molecules comprised of at least a portion of a human immunoglobulin light chain polypeptide sequence thereby producing said transgenic non-human animal.